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REVIEW

Epstein-Barr virus (EBV) status in colorectal cancer: a mini review

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ABSTRACT

Epstein-Barr virus (EBV) is a well-characterized oncovirus, associated with several malignancies. The complex and heterogeneous nature of colorectal cancer (CRC) has led to many epidemiological causal associations with CRC. However, a direct causal link between microbial infections and CRC has not been established yet. Our review indicates that the current evidence for the presence and role in EBV in CRC is insufficient and contradictory. The design of the analyzed studies, sample size as well as methodology used for EBV detection varied markedly and consequently may not lead to meaningful conclusions. The presence of EBV in other colorectal tumors (lymphomas, smooth muscle tumors) is in line with their status at other anatomic locations and may have therapeutic implications with EBV-specific vaccines. On the other hand, studies exploring EBV in colorectal adenoma-carcinoma sequence and its molecular genetic characteristics are largely missing and may significantly contribute to a better understanding of the role of EBV in CRC.

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Introduction

Colorectal cancer (CRC) is one of the major cancer problems worldwide due to its high prevalence and mortality rates. In most countries, CRC represents the third most common cancer and third leading cause of cancer-related deaths in both men and women.[1,2]

Advances in the pathogenesis, diagnosis and treatment of CRC have had a major impact on the overall management of CRC. These include substantial advances in CRC screening and prevention as well as advances related to novel biomarker and genomic analyses, personalized therapies and chemotherapy, which altogether have significantly affected the outcome of the patients with CRC. Despite these advances, many CRC patients, especially those with advanced and/or metastatic CRCs will eventually die of the disease.

Colorectal cancer (CRC) is a complex and multifactorial disease resulting from multiple interactions between hereditary, lifestyle, (epi)genetic, and environmental factors.[3] Among others, the concept of microbial-epithelial interactions as a potential oncogenic trigger for the development of CRC has also been proposed (reviewed by Collins et al.).[4] In contrast to gastric carcinoma and lymphoma (MALT type) both of which are strongly associated with *Helicobacter Pylori* infection,[4] a direct causal link between various microbial infections [e.g. *Helicobacter pylori, Streptococcus bovis, Escherichia Coli, Bacteroides*, JC virus, cytomegalovirus, human papillomavirus (HPV), Epstein-Barr virus (EBV)] and CRC has not been established yet.[4,5] The oncogenic effects of bacteria and viruses are different. Thus, bacteria may induce chronic inflammation or produce mutagenic toxins while most oncogenic viruses are small DNA viruses, which may interfere with the cell cycle of normal cells. Oncoviruses inhibit some key tumor suppressors such as *TP53* and *RB1* genes, avoiding the control of cell-cycle checkpoints and entering the S phase to replicate the viral DNA.[4]

Epstein-Barr virus (EBV) is the first recognized human oncovirus. It belongs to a group of gamma-herpes viruses and is ubiquitously present in the adult population, primarily via salivary transmission.[6] The estimated prevalence of EBV infection appears to reach > 90% of adults by the age of 35 years.[7,8]

The EBV genome consists of double-stranded DNA, whose length is approximately 172 kb.[6] It encodes viral oncogenes such as EBV-encoded nuclear antigens [EBNAs[1-3]] and latent membrane proteins [LMP[1,2]].[9] Interactions of EBV's surface protein gp350 with CD21 receptor and HLA class II on B-lymphocytes enables the entrance of the virus into B-lymphocytes.[6] Apart from B-cells, targets of EBV infection may include other human cell types such as epithelial cells as well as other hematopoietic cells (T cells, granulocytes, and natural killer cells).[8] However, the mechanisms of the infection of these cells may be different from CD21-mediated internalization, which is typically seen in B cells.[8]

The EBV exists in two different forms: latent and lytic replication.[10] In its latent form, the EBV DNA (enclosed in a circular plasmid) behaves like host chromosomal DNA. In contrast, in the replication (lytic) form, the EBV genome is dramatically amplified (up to 1000-fold) by EBV replication machinery. This process occurs at the replication compartments within the nuclei and the lytic program arrests cell cycle progression and affects the cellular processes significantly.[10] The lytic form of

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EBV infection is considered a mechanism through which EBV induces neoplastic transformation in EBV-associated malignancies (carcinomas and lymphomas).[10] However, latent EBV forms (e.g. EBNA-1, EBERs, LMP-1) may be present in various EBV-related malignancies such as Burkitt lymphoma, Hodgkin's disease and nasopharyngeal carcinoma.[8] EBV exhibits four types of latent gene expression, three of which (Latency I, II and III) have been described in EBV-related malignancies.[7] Latency I is usually associated with Burkitt lymphoma; Latency II has been found in Hodgkin's disease, T-cell non-Hodgkin's lymphomas and nasopharyngeal carcinoma whereas latency III predominantly affects immunocompromised patients (e.g. post-transplant and AIDS-related lymphoproliferative disorders).[8]

EBV causes infectious mononucleosis (benign, self-limited disease) and several lymphoproliferative and epithelial malignancies including B-cell lymphomas (Burkitt lymphoma, Hodgkin lymphoma, post-transplant lymphoproliferative disorder), T-cell/NK lymphomas, nasopharyngeal and gastric carcinomas.[11-13] In addition, EBV expression has also been demonstrated in several other carcinomas such as breast, prostate, oral, cervical and salivary gland carcinomas;[14-18] Nevertheless no causal relationship has been established yet.

Presently, data on the role and expression of EBV in colorectal cancer are sparse and contradictory without a clear evidence of the active role of EBV in colorectal carcinogenesis.[4] In addition, detection assays for EBV presence vary significantly across studies, which may have a significant impact on the obtained results.[4]

Here, we reviewed and critically appraised the studies reporting the status and the potential role of EBV in CRC carcinogenesis and other colorectal tumors with a possible link to EBV infection (lymphomas/lymphoproliferative disorders, smooth muscle tumors). We also explored the EBV status in CRC in relationship to its molecular genetic characteristics (e.g. mutational profile, microsatellite instability status). In addition, we analyzed the methodology used for EBV detection with emphasis on differences in EBV status between neoplastic and inflammatory (stromal) cells.

Methods

Search strategy and selection criteria

Data for this review were identified by searches of MEDLINE/PubMed/PubMed Central for the terms "Epstein Barr Virus", "EBV", "Colorectal cancer/carcinoma", "colon cancer/carcinoma", and "rectal cancer/carcinoma", and "colon tumors". Only articles/abstracts published in English were included in the review. The latest literature search was performed on July 1, 2018.

Results

The total number of extracted studies was 141. After careful evaluation and selection, only 50 articles were considered relevant for the present review (Figure 1). The remaining 91 studies were excluded as most of them were not focused on EBV in colorectal cancer but on other malignancies (e.g. gastric or head and neck carcinomas or malignant lymphomas/other lymphoproliferative diseases beyond the gastrointestinal tract), in addition to experimental studies exploring EBV and/or other viruses on non-colorectal cell lines.

Twenty-seven studies explored EBV status in CRC (summarized in Table 1). In addition, we found 23 studies (mainly

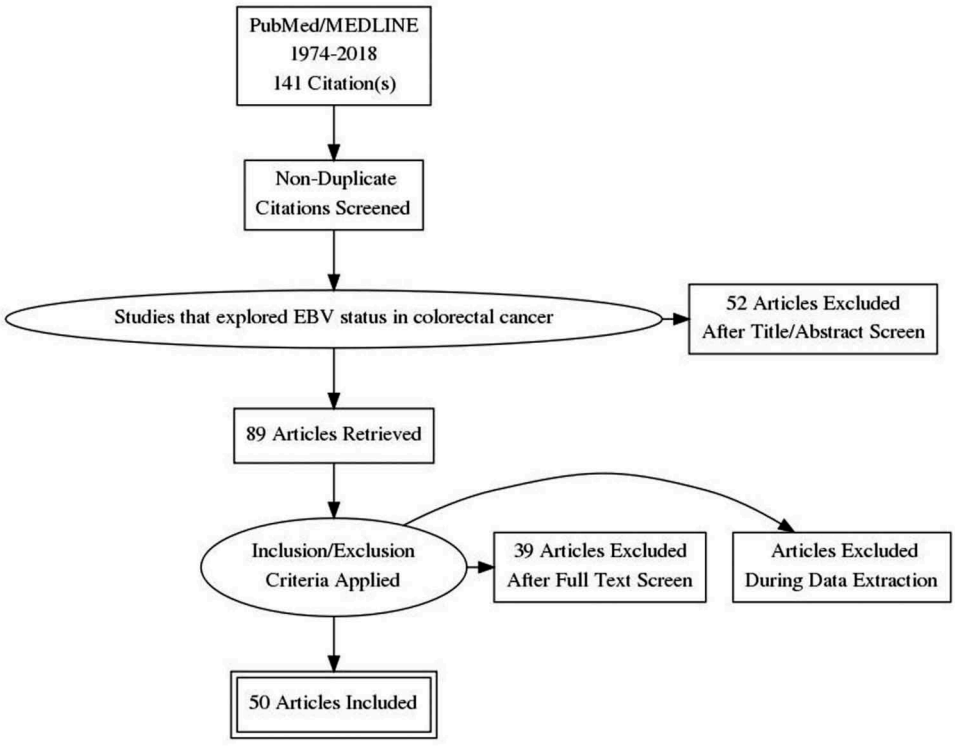

Figure 1. Flow diagram presenting the identified studies on PubMed/MEDLINE/PubMed Central on EBV and colorectal cancer.

Table 1. Studies (n = 27) that explored EBV status in colorectal cancer. The studies are listed in chronological order (from the newest to the oldest).

Study (Author/year)	Samples (number)	EBV status	Assay (detection method)	Other relevant findings/information
[19]	210 (including 70 colorectal carcinomas, 70 adenomas and 70 normal tissue samples)	1.4% positive carcinomas; all adenomas negative	PCR	The study also involved JCV and BKV viruses
[20]	102	36% positive	PCR and IHC	
[21]	35 (15 carcinomas and 20 adenomas)	0% positive	PCR	
[22]	Not applicable	Positive association	Multidimensional integration strategy	Data analysis based on gene expression profiling, protein-protein interactions, transcriptional and post-transcriptional regulation data
[23]	50	38% positive	PCR	
[24]	37	46% positive	PCR	The impact of viral load on metabolic and volumetric effects of cancer assessed by PET (^{18}F-FDG uptake), and CT
[25]	44	Negative in cancer cells but positive in lymphoid cells (52%)	RT-PCR and IHC	The study also involved other oncogenic viruses (polyomavirus (JCV, BKV, Merkel cell polyomavirus), HPV, HTLV, HHV-8 and EBV. The study revealed the presence of EBV in its latent form in tumor infiltrating lymphocytes.
[26]	117	21% positive	PCR	20% of samples were co-infected with other viruses (CMV and HHV-6B)
[27]	1	Negative	IHC	A case of LEC; the authors also reviewed previously published 5 cases of colon LEC of which only one had equivocal EBV positivity
[28]	1	EBV positive (serum)	PCR	Collision tumor (adenocarcinoma and DLBCL)
[29]	186	19% positive	PCR	No association between EBV and CpG island methylator phenotype (CIMP)-specific genes
[30]	72	30.6%	IHC and ISH	Colorectal cancers in renal transplant patients
[31]	1	negative	IHC	Concomitant colon adenocarcinoma and NHL
[32]	100 (2 cohorts)	2.8–39%	RT-PCR and sequencing	Multiple site analysis
[33]	1	negative	ISH	Cancer cells negative; inflammatory cells positive
[34]	90	~ 30%	IHC and ISH	
[35]	130	5% (IHC); 8% (ISH)	IHC, ISH, and PCR	
[36]	17 CRC + 9 NHL	CRC negative NHLs positive (6/9)	ISH	IBD-related colorectal carcinomas and lymphomas
[37]	19	5%	ISH	
[38]	1	Positive	PCR	LEC case
[39]	102	Negative	ISH	
[40]	274	Negative; TIL positive in 12.8%	ISH	
[41]	1	Negative by IHC, positive by PCR	IHC and PCR	LEC case
[42]	1	Tumor cells negative; TIL positive	ISH	
[43]	36	Negative	ISH	
[44]	13	Negative	PCR	
[45]	10	10%	DNA-DNA reassociation kinetics	

CRC = colorectal cancer; NHL = Non-Hodgkin lymphoma; LEC = Lymphoepithelioma-like carcinoma; IBD = Inflammatory bowel disease; DLBCL = Diffuse large B-cell lymphoma; EBV = Epstein-Barr virus; HHV = Human herpes virus; HIV = Human immunodeficiency virus; HTLV = Human T-cell leukemia virus type; IHC = Immunohistochemistry; ISH = In-situ hybridization; PCR = Polymerase chain reaction; RT-PCR = Reverse transcription PCR; PET = Position emission tomography.

case reports and small case series) exploring the EBV status in other colorectal malignancies, predominantly in lymphoproliferative diseases [Hodgkin lymphoma and non-Hodgkin lymphomas (B- and T-cell lineage)] and other rare large bowel tumors (e.g. smooth muscle tumors and inflammatory pseudotumor-like follicular dendritic cell sarcoma) (summarized in Table 2).

Status of EBV in colorectal cancer

A summary of the identified studies (n = 27) with key findings is presented in Table 1. The methods used for EBV detection in human samples (blood, tissues) included immunohistochemistry (IHC), in situ hybridization (ISH), and PCR-based assays. Several studies used combined assays (IHC and ISH) (see Tables 1 and 2).

The current literature review reveals a contradictory data on the presence of EBV in colorectal cancer samples. Thus, a positivity rate for EBV is CRC varies in a broad range from 0% (reported by[21,27,39,40,43,44] up to 46% reported by Sole et al.[24] The largest single study (n = 274 samples) conducted by Cho et al.[40] using immunohistochemistry failed to detect EBV in cancer cells in any of the tested cases. However, they found tumor-infiltrating lymphocytes (TIL) to be positive in 12.8% of the cases. Studies of Vilor et al.,[42] Fiorina et al.[25] and Kojima et al.[33] also reported only TILs to be positive in CRC samples.

Most positive studies revealed EBV positivity rate to be ~ 20–40% of the cases.[20,23,26,29,30,32,34] A study of Salyakina et al.[26] reported a common co-infection of EBV with other viruses in 20% of the CRC samples (Cytomegalovirus and Human Herpesvirus 6B/HHV-6B/). An interesting case study by Chang et al.[28] on collision colorectal tumors (adenocarcinoma and non-Hodgkin lymphoma) revealed serum

Table 2. Studies (n = 23) that explored EBV status in other colorectal malignancies/disorders. The studies are listed in chronological order (from the newest to the oldest).

Study (Author/ year)	Samples (tumor type and number)	EBV status	Assay (detection method)	Other relevant findings/information
[46]	Inflammatory Pseudotumor-like Follicular Dendritic Cell Sarcoma (1)	Negative	PCR	
[47]	DLBCL (1)	Positive	IHC	
[48]	T-cell lymphoproliferative disease (1)	Positive	PCR	
[49]	Plasmablastic lymphoma (1)	Positive	IHC	HIV-negative patient
[50]	EBV-positive mucocutaneous ulcers (1)	Positive	ISH	EBV-associated lymphoproliferative disease with progression to HL in a patient with Crohn's disease
[51]	HL (1)	Positive	ISH	Rectal HL in a patient with UC
[52]	HL (1)	Positive	ISH	Anorectal Hodgkin lymphoma in a HIV-negative patient
[53]	B-cell lymphoma (1)	Positive	IHC	A patient with IBD
[54]	Smooth muscle tumors in post-transplant pediatric patients (2)	Positive	ISH	Smooth muscle tumors in post-transplant pediatric patients
[55]	HL (1)	Positive	IHC	Rectum
[56]	HL (1)	Negative	ISH	A patient with UC and primary sclerosing cholangitis
[57]	EBV-associated cecal post-transplant lymphoproliferative tumor (1)	Positive	PCR	EBV-associated cecal post-transplant lymphoproliferative tumor
[58]	NK/T-cell lymphoma (1)	Positive	ISH	Rectum (patient with refractory UC)
[59]	DLBCL (1)	Positive	ISH	Methotrexate-associated DLBCL
[60]	HL (1)	Positive	IHC and ISH	A patient with Crohn's disease
[61]	Smooth muscle tumor (1)	Positive	IHC, ISH, PCR	EBV-related post-transplant lymphoproliferative and smooth muscle neoplasm (PTSN)
[62]	B-cell lymphoma (1)	Positive	IHC	A patient with the steroid-refractory UC
[63]	HL (1)	Positive	ISH	Rectum
[36]	Seventeen CRC and nine NHL cases	CRC negative NHLs positive (6/9)	ISH	IBD-related colorectal carcinomas and lymphomas
[64]	T-cell lymphoma (1)	Positive	ISH	
[65]	HL (4)	Positive	IHC and ISH	Association with IBD and immunosuppression
[66]	Small muscle tumors (3)	Positive (100%)	IHC and ISH	Small muscle tumors following transplantation
[67]	B-cell lymphoma (1)	Positive	Serology	In a patient with HIV and HTLV-1 co-infection

CRC = colorectal cancer; NHL = Non-Hodgkin lymphoma; IBD = Inflammatory bowel disease; UC = Ulcerative colitis; DLBCL = Diffuse large B-cell lymphoma; HL = Hodgkin lymphoma; EBV = Epstein-Barr virus; HTLV = Human T-cell leukemia virus; HIV = Human immunodeficiency virus; IHC = Immunohistochemistry; ISH = In-situ hybridization; PCR = Polymerase chain reaction.

EBV positivity. However, the authors did not examine the EBV presence in cancer cells of either malignancy. Wong et al.[36] studied IBD-related colorectal carcinomas and lymphomas (n = 26) using in-situ hybridization assay (ISH). They confirmed the EBV presence in 66% of non-Hodgkin lymphomas but failed to detect it in colorectal carcinoma samples.

Mehrabani-Khasraghi et al.[21] explored EBV in both colon adenomas and carcinomas. The authors used PCR to examine 35 colon samples (Fifteen CRCs and twenty adenomas) and failed to detect any positive cases. Similar results were obtained in a study by Sarvari et al.[19] (Table 1).

The study of Karpinski et al.[29] was based on the fact that integration of viral genome into the host may cause alterations of the methylation pattern, which is a common molecular event in CRC pathogenesis.[68] Although they found EBV in 19% of the tested samples (n = 186), EBV presence along with the John Cunningham virus (JCV) were unrelated to the methylation status of the six CpG island methylator phenotype (CIMP)-specific genes (*MLH1, CACNA1G, NEUROG1, IGF2, SOCS1, RUNX3*) and seven cancer-related genes (*p16, MINT1, MINT2, MINT31, EN1, SCTR* and *INHBB)*.[29] On the other hand, a study by Park et al.[30] assessed the EBV status in colorectal cancers in renal transplant patients. They found EBV in 30% of the samples using immunohistochemistry and in-situ hybridization assays. Similarly, Albright et al.[57] reported EBV-positive post-transplant lymphoproliferative tumor of the cecum (Table 2). Elawabdeh et al.[54] reported two EBV-positive small muscle tumors of the colon in the post-transplant pediatric patients. Lee et al.[66] reported similar findings in three post-transplant patients with small muscle tumors of the colon.

Another type of primary colorectal cancer is lymphoepithelioma-like carcinoma (LEC) or poorly differentiated adenocarcinoma with lymphoid stroma, which is an extremely rare subtype.[41] LEC of the colon is morphologically similar to poorly differentiated nasopharyngeal carcinomas that are strongly associated with EBV infection.[69] Nevertheless, a study of Delaney et al.[27] involving a case of LEC of the colon revealed no EBV presence. The authors also reviewed previously published five cases of colon LEC of which only one case had equivocal EBV positivity.[27] A study of Samaha et al. involving one LEC revealed no EBV in cancer cells by IHC but only by PCR.[41] This discrepancy may reveal the potential bias caused by DNA contamination by EBV-positive inflammatory cells in PCR assays, while IHC, enables a precise identification of the location of EBV presence (cancer vs. inflammatory and/or stromal cells). Thus far, Kon et al.[38] conducted the only study that confirmed EBV presence in cancer cells of the colon LEC. Taken together, the results on EBV in LEC of the colon are strikingly different from those on EBV of the LECs affecting other anatomic locations, e.g. lacrimal and salivary glands, esophagus, pancreas and middle ear.[70-75] Notably, our recent review on LEC of uterine cervix revealed no EBV infection in cancer cells in this rare primary cervical malignancy[76] .

Status of EBV in hematologic malignancies and other tumors of the colon

A summary of the identified studies (n = 23) with key findings is presented in Table 2. Given that the primary non-epithelial malignancies of the colon are very rare, it is not surprising

that most of the published reports are either case reports or small case series. A vast majority of EBV-positive colorectal non-epithelial malignancies are hematological malignancies, predominantly lymphomas, both Hodgkin and non-Hodgkin of B-, T- and NK-origins (Table 2). Hodgkin lymphoma (HL) is a well-known hematologic malignancy, associated with EBV infection in 50% of the cases (particularly lymphocyte-depleted and mixed-cellularity variants). HLs are characterized by the presence of Reed-Sternberg (RS) cells, typical B-transformed malignant cells, which are infected by EBV. In addition, EBV has been demonstrated in other hematologic malignancies such as Burkitt lymphoma, post-transplant lymphoproliferative disorders, and various T-cell/NK lymphoproliferative disorders. Therefore, it is expected that EBV-associated hematologic malignancies located in the colon are frequently EBV positive as their counterparts elsewhere in the body (Table 2).

Specifically for colon, several studies explored the EBV status in lymphoproliferative neoplasms in association with inflammatory bowel disease (IBD) (Crohn's disease and ulcerative colitis). Most of these studies confirm EBV presence in lymphoproliferative diseases associated with IBD.[36,50,51,53,58,60,62,65] Van Hauwaert et al.[56] reported the only case of EBV-negative Hodgkin lymphoma in a patient with ulcerative colitis and primary sclerosing cholangitis.

EBV status in smooth muscle tumors of the colon was explored in three separate small studies (total number of patients was six, predominantly pediatric, post-transplant patients).[54,61,66] All three studies confirmed the presence of EBV (100%) in this rare primary colon tumor.

Discussion

Although some comprehensive association studies revealed a positive association between EBV infection and CRC,[22] based on data analysis from gene expression profiling, protein-protein interactions, transcriptional and post-transcriptional regulation data; Nevertheless, currently, scientific evidence for the presence and role in EBV in colorectal cancer is insufficient and contradictory. The design of the analyzed studies (retrospective nature, selection bias), sample type (paraffin-embedded tissue block vs. fresh tissue; endoscopic vs. surgical biopsy), sample size (small cohorts), disease stage as well as the methodology used for EBV detection varied markedly and may not consequently lead to any meaningful conclusions. Several studies reporting a positive association were based on PCR assay, which may be contaminated by EBV-positive inflammatory cells, but not cancer cells. In addition, the role of EBV in tumor infiltrating cells (lymphocytes) is unclear; some well documented studies (e.g. Fiorina et al.)[25] revealed the presence of EBV in its latent, not lytic form in lymphoid aggregates within the tumor mass, which led the authors to argue against the active oncogenic role of EBV in colorectal carcinogenesis.

A substantial proportion of the analyzed studies (8/27) used immunohistochemistry (IHC) alone or combined with other techniques for EBV detection. Since EBV assessment by IHC is not routinely employed in CRC and other colorectal malignancies, the thresholds for positivity varied across the studies (1–10%) while several studies did not report the threshold for positivity.[20,25,27,30]

We point out here the importance of the method of EBV detection as it may play a key role in elucidating not only the presence but also the potential contribution of EBV to colorectal carcinogenesis. Most studies used PCR and/or IHC for EBV detection. Given that both assays may be biased by only selecting/targeting a certain EBV gene (due to different primers) or protein (different antibodies), therefore, more state-of-the art methods with higher sensitivity would avoid such biases should they be applied to detect EBV in colorectal and other cancers.[77] A less biased approach should include a full sequencing of colorectal cancer cells and search for any EBV nucleic acid fragments present. One such methodology that allows for an unbiased approach is next-generation sequencing (NGS) assay, a recent high-throughput DNA assay.[77] Likewise, other PCR-based techniques and NGS assays are not necessarily devoid of the contamination by infiltrating immune cells (lymphocytes), which implies that additional approaches (e.g. microdissection of cancer cells or single cell analysis) may help in circumventing the detection bias. A number of different NGS platforms are currently available for diagnostic and theranostic purposes and their detailed discussion is beyond the scope of this article.

Therefore, we believe that studies exploring EBV presence and role in colorectal adenoma-carcinoma sequence are largely missing and may significantly contribute to a better knowledge on the role of EBV in colorectal carcinogenesis. A recent study of Sarvari et al.[19] revealed very low EBV positivity in invasive colorectal carcinomas (1.4%) while all corresponding colorectal adenomas (n = 70) as well as adjacent normal colonic mucosa (n = 70) were negative for EBV. Similarly, Mehrabani-Khasraghi et al[21] reported no EBV expression in any carcinomas or adenomas they investigated. In addition, studies exploring the relationship between EBV presence and molecular genetic characteristics of CRC (e.g. mutational profile, microsatellite instability status, immune status, e.g. checkpoint regulators PD-1 and PD-L1) are completely missing. Primary non-epithelial cancers affecting colon are very rare. Most non-epithelial colon malignancies are hematologic cancers (lymphomas) some of which may be associated with IBD. In this regard, it is well known that immunosuppressive drugs used for the treatment of IBD and organ transplant recipients may reactivate viral diseases such as EBV and trigger their oncogenic role in the development of various malignancies.[78] Our review confirms that the EBV-status in lymphoproliferative disorders affecting colon is similar to those occurring elsewhere in the body (e.g. classical Hodgkin lymphoma and other B-cell lymphomas/lymphoproliferative disorders may be EBV positive in a significant proportion of the cases).[79] Interestingly, EBV presence was also confirmed in six cases of smooth muscle tumors of the colon including those affecting post-transplant pediatric patients.[54,61,66] This is in line with EBV positivity in smooth muscle tumors at other anatomic locations, particularly among the immunocompromised and/or post-transplant patients (e.g. head and neck, vulva).[80-83] The presence of EBV in non-epithelial colonic tumors may also have therapeutic implications given the recent success with an EBV specific vaccine that was successfully used in the treatment of EBV-positive nasopharyngeal carcinoma.[84,85] Another

alternative for the treatment may be the prophylactic EBV vaccine, which is based on virus-like particles that mimic the structure of EBV but lacks EBV genome. This approach has been shown to be effective in preclinical models.[86]

Conclusions

The current scientific evidence for the presence and role of EBV in colorectal cancer pathogenesis is insufficient and contradictory. The design of the analyzed studies, their sample size as well as the methodology used for EBV detection vary markedly and may not consequently lead to meaningful conclusions. Several studies reporting positive associations were based on PCR assay, which may be contaminated by EBV-positive inflammatory, but not cancer, cells. In this regard, the presence of EBV in inflammatory cells (lymphocytes) may not be an indication of an oncogenic effect given that the virus may be in its latent form. Apparently, high sensitivity assays (e.g. NGS platforms) that allow for a full sequencing of colorectal cancers for any EBV load are critically important to elucidate the potential contribution of EBV in colorectal oncogenesis. The presence of EBV in other colorectal tumors (lymphomas, smooth muscle tumors) is in line with the EBV status in these tumors at other anatomic locations. Nevertheless, studies exploring EBV presence and role in colorectal adenoma-carcinoma sequence are largely missing and may significantly contribute to a better knowledge on the possible role of EBV in colorectal carcinogenesis. In addition, studies exploring the relationship between EBV and molecular genetic characteristics of CRC (e.g. mutational profile, microsatellite instability status, immune checkpoint regulators/PD-1 and PD-L1) are also warranted. Most non-epithelial colon malignancies are lymphoproliferative diseases (lymphomas) some of which may be associated with inflammatory bowel disease. Their EBV-status in colon is similar to those occurring elsewhere in the body and unrelated to inflammatory bowel disease. In any case, future studies are necessary to confirm the importance of EBV vaccines in the treatment of such malignancies.

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Disclosure of potential conflicts of interest

No potential conflict of interest was reported by the author.

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